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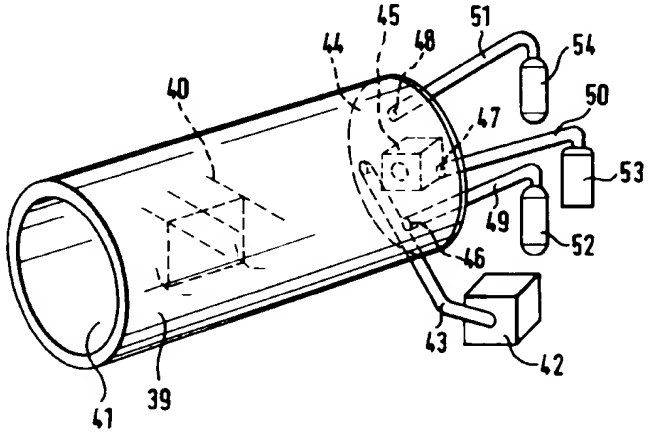
(54) Method for pretreating the surface of a medical device.

(57) A method for pretreating the surface of a medical device, and of applying a polymer coating, in order to apply a biological coating in a further step, uses the plasma polymerization technique or the plasma grafting technique. A functional monomer, i.e. a monomer with a functional group, or a mixture of a pure monomer and a substance able to provide the required functional groups under spark discharge or under the influence of charge carriers, results in a polymer coating with free functional groups, which may react with the biological coating, thus providing optimum adhesion of the biological coating. The process is carried out in a pressure-tight chamber (39) with an inlet (48) for the functional monomer under low pressure and electromagnetic radiation provided by a radiation source (45).

Fig. 9



EP 0 519 087 A1

The present invention relates to a method of pretreating the surface of a medical device intended for appliance of a biological coating, and for applying a biological coating to the surface of such medical device, according to the preambles of claims 1 to 4.

A common problem in medical devices intended for blood contact is the biocompatibility of the surface of such devices. Medical devices, such as artificial heart valves, are often in permanent or at least long-lasting contact with human or animal blood. By the way, this does not only apply to medical devices implanted or otherwise introduced into the human or animal body, but also to medical devices used in extracorporeal systems like a heart-lung machine.

If no special care is taken, the contact between the medical device and the blood may result in so-called "clotting" (coagulation) at the surface of the medical device. Such clots may render the medical device (e.g. a sensor) inoperable. Further, they may reduce the free-space sectional area of a blood vessel, therefore reducing blood flow. Even worse, a clot formed on the surface of the medical device may be detached by the flowing blood and occlude a blood vessel (in particular, a capillary) thus causing thrombosis.

The situation is even more critical in case of a catheter or an intravascular blood gas sensor introduced in a blood vessel of relatively small diameter such as the radial artery or the femoral artery. The catheter may be completely blocked by a clot, so that the blood pressure cannot be measured or that no blood samples can be taken; in case of an intravascular blood sensor, the active area may be blocked (i.e. no fresh blood can reach the sensor).

The above considerations are of particular importance when long-term contact between the medical device and the blood is intended. Even with optimum material selection for the medical device, clotting cannot be reliably prevented.

A common approach to solve this problem, i.e. to prevent the formation of clots, is to coat the medical devices with a biological coating (sometimes also referred to as bioactive or antithrombogenic coating). Coatings suited for this purposes are well-known in the art. For example, a heparin-based coating, such as described in United States Patent U.S. 4,810,784, may be used. Other suitable biocompatible materials are e.g. phosphorylcholine (EP-B-157 469) or polyester (U.S. 4,792,599). Hirudin may be used as well. Further biological coating materials useful as anticoagulants are known in the art.

A common problem when applying such biological coatings to a medical device is to ensure reliable adhesion between the coating and the surface of the medical device, i.e. reliable immobilization of the coating. It is understood that a bad contact would lead to detachment of the coating, so that the medical device looses its antithrombogenic properties. As the biological coating does not adhere to the surface of the medical device by itself, additional measures have to be taken. Further, it has to be ensured that the biological coating does not loose its bioactive properties during the immobilization process.

A known solution to this problem is to coat the surface of the medical device with a polymer and to apply the biological coating to the polymerized surface. For this purpose, the pure (uncoated) medical device is put into a polymer bath, i.e. a solvent containing dissolved polymer. When the medical device is removed, its surface carries a thin film of solvent containing the polymer. The solvent then vaporizes, such that the pure polymer resides on the surface of the medical device. Subsequently, the biological coating is applied, e.g. by putting the medical device into an appropriate bath.

However, the immobilization of a biological coating fastened on the surface of a medical device in this manner is not always reliable. The inventor in the present case has particularly noted that parts of the biological coating detached in use from an intervascular blood gas sensor. This has particularly happened when a medical device is stored or deposited in a liquid for a longer time period (e.g. an intravsacular sensor requiring a wet or liquid environment to keep its operability even when not in use). Such detachment is an untolerable disadvantage of the known technique, partially because of the danger for the patient as blood clots may attach to the uncoated portions of the surface, and partially as such removal of the biological coating may affect the measuring accuracy of the sensor when parts of it are coated and others are not.

It is therefore a major objective of the present invention to provide a method for reliable attachment of a biological coating to the surface of a medical device.

According to one aspect of the invention, this object is solved by performing the following steps:

1. The medical device is exposed to a chemical agent consisting of monomer molecules chemically combined with functional groups, said chemical agent being present at least in its gaseous state;
2. electromagnetic waves, in particular in the radio frequency range, are irradiated into said chemical agent and/or onto the surface of said medical device until the molecules of said chemical agent constitute a functional polymer on the surface of the medical device, and
3. the biological coating is applied to the surface of the medical device.

The invention makes use of a basically well-known technique called "plasma polymerization". According to this technique, the object to be coated with a polymer is put in a pressure-tight chamber. Monomeres in gaseous form are then conducted into the chamber. A source of electromagnetic radiation irradiates high-frequency waves into the chamber, thereby creating a plasma (i.e. a gas containing free radicals). Even during spark discharge, temperature in the chamber is only slightly increased.

The plasma thus created allows the monomeres to polymerize on the surface of the object. The polymer forms a thin layer on the surface, just like a very thin hose or tube.

In the light of the unsatisfying results obtained with the above described technique of applying dissolved polymers to the surface of the medical device, the inventor has investigated usual (e.g. thermal) polymerization techniques (thermolysis, photolysis, use of radical starters); i.e. techniques wherein no polymer molecules are applied to the surface, but monomeres instead, and polymerization is then effected. This could be an attractive approach as the single polymer molecules are more effectively "muddling" thus leading to increased consistency.

However, even these usual polymerization techniques did not produce a satisfying result. Attempts have then been made with the above described plasma polymerization technique, but also with limited success.

But then, the inventor has surprisingly found that the desired effect can be achieved if not simple monomeres (as have been used in prior art techniques) are used, but monomeres with an additional functional group instead. In fact, plasma polymerization of monomeres with a functional group resulted in a coating which was able to keep the biological coating very reliably in place. Studies have shown that the biological coating does not detach from polymeres produced in this way, even in long-term use.

The present invention thus overcomes the disadvantages of the prior art. In particular, medical devices coated with a first polymer coating according to the invention and a second (biological) coating have proven to operate very accurate (i.e. their operation is not impaired by the coating). This is e.g. important for medical sensors, since the sensor reading should not be influenced by either coating. Still the biological coating does adhere to the surface of the medical device over very long time periods, so that thrombosis and other negative effects are avoided. This is particularly due to the functional groups of the polymer which adhere chemically to the biological coating. ("Functional polymer" as used herein means a polymer with functional groups.) Further, the biological coating is able to resist considerable mechanical stress.

Although made when investigating the biological coating of an intravascular blood gas sensor, and although the invention is particularly suited for such sensor, it is understood that the inventive method may also be applied to a variety of other medical devices intended for blood contact, such as artificial blood vessels, heart valves, catheters and the like. Intravascular blood gas sensors as such are basically known in the art, see e.g. EP-B-279 004, EP-B-336 984 and EP-A-336 985; the full content of these publications is hereby incorporated into the disclosure of the present invention by reference.

In the case of an intravascular blood gas sensor, the "plasma" coating generated by the inventive method has further advantages. In particular, such sensor consists of a variety of materials, e.g. the coating of the single sensors, the semipermeable membranes covering their diffusion zones, a sheath etc., which are all in blood contact. Therefore, if the biological coating would be directly applied to the sensor, it would cover areas of different consistency and different physical properties; it could thus happen that the biological coating does not behave in a uniform manner. E.g. its resistance to the accumulation or adhesion of clots could be varying, dependent on the covered material, or it could detach from certain areas only and remain on other areas (the latter effect is particularly disadvantageous as a limited detachment, e.g. restricted to several square micrometers, is difficult to detect, but still dangerous for the patient). These problems and disadvantages are overcome by the present invention, as it is now possible to provide a uniform and reliable polymer coating, so that the biological coating adheres to a uniform material.

It is a further advantage of the inventive method that it can be implemented very easily and in a cost-effective manner. This is because a basically known apparatus can be used to effect plasma polymerization, so the only basic modification is the use of monomeres with an additional functional group.

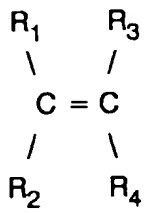
To apply the polymer coating, the medical device is put in a closed, preferably pressure-tight chamber. The gaseous chemical agent consisting of monomer molecules chemically combined with functional groups is then allowed to stream into said chamber through an appropriate opening or valve, preferably from a container or the like filled with said chemical agent. Next, a source of radiation energy is switched on. This source may be arranged at a side wall of the chamber or in an annular arrangement around the chamber (which preferably has a cylindrical cross section). Other suitable arrangements of the radiation source may be used as well. Because of the high intensity of the radiation, an electrically shielded chamber is preferred. In an advantageous embodiment, the emitted electromagnetic waves are in the radio frequency spectrum; specifically, a frequency of 13.56 MHz (MegaHertz) has been used. The electromagnetic waves are irradiated into the chamber, and the spark discharge causes the gaseous chemical agent to form a

"plasma", e.g. a gas with free radicals. This allows the monomeres with their respective functional groups to form a polymer which covers the surface of the medical device.

The biological coating may then be applied to the polymer-coated surface in basically known manner. I.e. it is not necessary to apply the biological coating immediately to the polymer coating in order to satisfy free bondings of the polymer. Instead, the polymer-coated medical device may be removed from the chamber and then put into a chemical bath in order to apply the biological coating. It is even not necessary that the step of applying the biological coating is performed immediately after the appliance of the polymer coating; instead, the biological coating may be applied weeks later. The appliance of the polymer coating and the biological coating are chemically "separate" steps. Therefore, the present invention does not only relate to the combination of applying a polymer coating and a biological coating, but also to a method for pretreating the surface of a medical device according to claim 1, i.e. it relates to the steps necessary to apply a polymer coating, in preparation of the appliance of the biological coating itself.

The process of plasma polymerization may be significantly improved by the use of underpressure, i.e. a pressure below atmospheric pressure. This can be achieved by a pressure-tight chamber which is approximately evacuated. Advantageously, the pressure is reduced until it is in a range from 0.01 millibar to 10 millibar, and more specifically, in a range from 0.1 millibar to 1 millibar. In one embodiment of the invention, a pressure of 0.3 millibar ($3 * 10^{-4}$ bar) has been applied to the chamber, for a duration of around 20 minutes and with a RF (radiation frequency) power of 30 mW (milliwatts), with excellent results.

As outlined above, the used chemical agent consists of monomeres incorporating functional groups. The wording "monomer molecules chemically combined with functional groups" used herein means that each (or at least the majority of) monomer molecules is combined with or bound to at least one functional group. Monomeres as the basis for polymerization as such are well-known in the art. A common basic structural formula for monomeres is



(1)

wherein R_n denotes hydrogen atoms, halogen, halide or organic residues or radicals (see for example Alfred Kemper/Rüdiger Fladt, Chemie, Stuttgart 1968, p. 290).

According to the present invention, the used monomeres are further chemically combined with (bound to) functional groups. Such functional groups are at least partially kept during the plasma coating process and result in a functional polymer which can covalently bind to other molecules (this process will be described in detail below). In a general sense, a functional group is a chemically active or reactive group (responsive to substitution or rearrangement), and more specifically, a functional group can be defined as a group which tends to amide formation, amine formation, acid formation, esterification, etherification etc.

There are several functional groups which have been found advantageous. A preferred group is e.g. the amino group, $-NH_2$. Each monomer molecule may be combined with one or more amino groups. (It is understood that further groups, radicals etc. may also be chemically bound to such a "functional monomer"). A typical useful chemical agent consisting of a monomer and an amino group ("functional monomer") is allylamine, $H_2C=CH-CH_2-NH_2$. The surface of the medical device polymerized with allylamine comprises free amino groups, which in turn may bind to the molecules of the biological coating (see below). Another chemical agent of this kind is 4-amino-1-butene, $H_2C=CH-CH_2-CH_2-NH_2$. It is understood that other olefins with additional amino groups are advantageous as well (in general: $H_2C=CH-(CH_2)_n-NH_2$, $n=0,1,2,...$).

Instead of using an olefin with appended amino group, it is also possible to use a pure olefin and to add ammonia, NH_3. That is, a physical mixture of these substances is used rather than a chemical compound. Such mixture produces a polymer coating with free amino groups on the surface of the medical device as well.

Another useful functional group is the carboxyl group, -COOH. The respective chemical agents (monomer plus functional group) are therefore preferably unsaturated carboxylic acids, e.g. acrylic acid ($H_2C=CH-COOH$), butenoic acid ($H_2C=CH-CH_2-COOH$), pentenoic acid ($H_2C=CH-CH_2-CH_2-COOH$), and so on. The general chemical formula for such unsaturated carboxylic acids is $H_2C=CH-(CH_2)_n-COOH$

(n = 0,1,2,...).

The -OH group as such has also been found to be suited as functional group. A typical chemical agent (monomer plus functional group) of this kind is ally alcohol, $H_2C = CH\text{-}CH_2\text{-}OH$. The general group of alcohols useful for the present invention can be given by the formula $H_2C = CH\text{-}(CH_2)_n\text{-}OH$, n = 0,1,2,...

It should be noted that the above formula (1) does not cover all possible types of monomeres. For example, a monomer with triple bond, i.e. a monomer with the general structural formula

$$R_1 - C \equiv C - R_2 \qquad (2)$$

could be used in the present invention as well. An example of such a monomer with additional functional group (in this case, an amino group) is $HC\equiv C\text{-}CH_2\text{-}NH_2$ (3-amino-1-propine); the general notation for the class of amino compounds of this type is $HC\equiv C\text{-}(CH_2)_n\text{-}NH_2$, n = 0,1,2,...

The most general definition of a monomer is a substance which is able to polymerize. Formulae (1) and (2) are thus limited generalizations only and do not cover all possible types of monomeres.

It will be appreciated that the examples of chemical agents, monomeres and functional groups described above, although they have proven very useful for the present invention, relate to preferred embodiments only, and that the skilled man may be able to identify other chemical agents, monomeres or functional groups suited for this invention. The above examples illustrate that there is a large variety of chemical agents, even of basically different constitution, fulfulling the needs of the invention.

It will further be appreciated that, instead of applying a chemical agent consisting of monomer molecules chemically combined with functional groups to the surface of the medical device, it is also possible to apply the pure monomer and to accomplish its desired chemical composition with a functional group in the plasma, i.e. under electromagnetic radiation. In this case, a substance has to be added to the pure monomer which is able to form a functional group under radiation, which then combines with the pure monomer. The "chemical agent" referred to above is thus created *in situ* as an intermediate product, which then reacts in the described manner, i.e. by forming a functional polymer on the surface of the medical device. That is, although the process is started with a physical mixture instead of a chemical compound, its result, and even the second step, are the same as if a chemical composition were used.

One example of this kind has already been described above. This was the physical mixture of a pure olefin and ammonia, which then forms a chemical compound with an $-NH_2$ group under the influence of radiation. Other substances which may be physically added to the monomer are e.g. carbon dioxide (CO_2) in case a carboxyl group is intended to be chemically bound to the monomer as an intermediate product, or water (H_2O) in case the intermediate product should comprise an -OH group. Other such substances useful to create suitable functional groups are available to the skilled man.

In an alternative embodiment of the invention, the so-called plasma grafting technique (in contrast to the plasma polymerization technique described above) is used. This technique comprises two basic steps: In the first basic step, a chemically inert gas (e.g. a noble gas such as argon, helium or neon) is applied to the medical device, and the source of electromagnetic radiation is turned on. This creates or induces charge carriers in the surface of the medical device. These charge carriers remain present even when the source of radiation is switched off.

In the second basic step, the medical device is exposed to a chemical agent of the same constitution as in the plasma polymerization technique (if the process is performed in a closed chamber, the inert gas is removed by suction, and the chemical agent is allowed to stream into the chamber). However, in this second step, the source of electromagnetic radiation, i.e. the spark discharge, is switched off. The charge carriers in the outer layers of the surface of the medical device however initiate the polymerization process.

The major advantage of the plasma grafting technique is that the ends of several polymer chains are covalently bound to the surface of the medical device. That is, there is also a chemical bonding between the surface of the medical device and the polymer coating, not only between the polymer coating and the biological coating. This further reduces the probability that the biological coating, with or without polymer coating, may detach from the surface of the medical device.

A further advantage of the plasma grafting technique is that shorter polymer chains are created. The monomeres do not or hardly polymerize among each other, but on the surface of the medical device only, so that the process is more effective.

It is understood that a physical mixture of a pure monomer and a substance which is able to form the required functional group during or just immediately prior to the polymerization process may also be used when performing the plasma grafting technique. However, a slight distinction to the plasma polymerization technique has to be noted in this case. The functional monomer consisting of monomer molecules with additional functional group is formed during the second step of the plasma grafting process *in situ*, i.e.

when the radiation source is switched off. This means that a monomer and a substance have to be used which are able to combine chemically under the influence of the charge carriers created in the first step (appliance of inert gas and spark discharge), instead as under spark discharge as in the plasma polymerization technique. However, most monomeres and substances used in the plasma polymerization technique may also be used for the plasma grafting technique, and the skilled man will be able to identify further suited substances.

In an advantageous embodiment, a further method step is added to the plasma polymerization technique or the plasma grafting technique. This further step is performed prior to any of the polymerization steps. It consists of exposing the medical device to a chemically active (aggressive) gas, such as oxygen, and switching the source of radiation on. During spark discharge impurities, e.g. dust, residues left by fingerprints etc., are sparked until the surface of the medical device is substantially clean from such impurities. The additional step of cleaning the surface has the further advantage that additional charge carriers are created in the outer surface of the medical device. However, in contrast to the plasma grafting technique, the charge carriers created during the purifying process recombine quite quickly as soon as the radiation source is switched off and the purifying gas (chemically active gas) is removed. This effect may be prevented in that the purifying gas is immediately replaced by an inert gas, e.g. by flushing the purifying gas out with the inert gas.

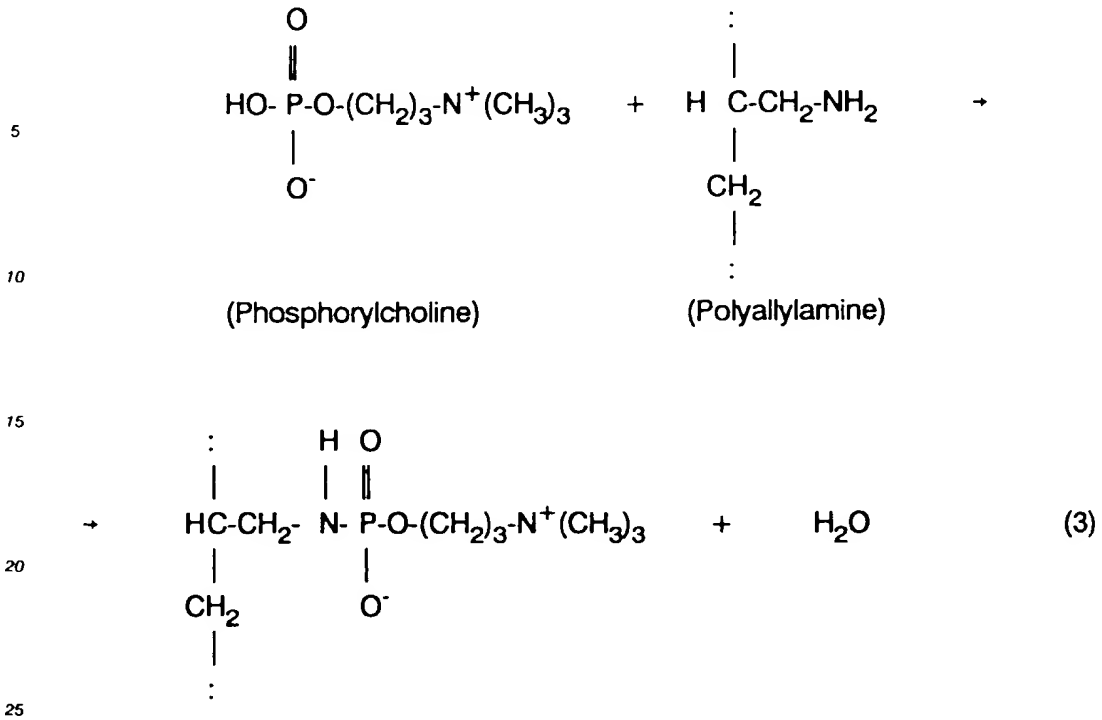
One may imagine that the above process steps may be combined in any suitable manner, dependent on the equipment and the requirements of the application. For example, the plasma polymerization technique may be used, with or without prior purifying step. Further, the plasma grafting technique may or may not be combined with the purifying step. In a preferred embodiment, incorporating the plasma grafting technique with prior purification, the inventive method comprises therefore three different states of the process:

1. Apply chemically active gas (e.g. oxygen), switch on radiation - the surface of the medical device is purified by sparking, and temporary charge carriers are created in the outer surface.
2. Flush the chemically active gas out by an inert gas (e.g. argon) while the radiation source is still operating - the temporary charge carriers created during step 1 are thus made "quasi-permanent", i.e. become charge carriers with a considerably longer lifetime, and further charge carriers are created.
3. Flush the inert gas out with a functional monomer (monomer with functional groups), switch off source of radiation - the charge carriers in the outer surface of the medical device start the polymerization. By the way, the inert gas may also rarify the functional monomer.

As outlined above, step 3 could be replaced by flushing with a mixture of a pure monomer and a substance, such as ammonia, so that the functional monomer is created just prior to polymerization ("*in situ*").

It is a goal of all the various techniques described above to establish a functional polymer coating on the surface of the medical device which is able to chemically react with the biological coating, i.e. to have the functional groups of the polymer bind to certain molecules of the biological coating. A method of binding heparin to $-NH_2$ groups is e.g. described in the above-mentioned United States Patent US 4,810,784 wherein the amino groups are reacted with "fragment" heparin carrying a terminal aldehyde group to a Schiffs base, which is then, by reduction, converted to a secondary amine (it has to be noted that the results of this prior art technique are not always reliable if no further measures are taken. This may be caused by the fact that functional polymeres are directly (i.e. without polymerization) applied to the surface of a device by vaporizing the solution in which the polymer is dissolved, as described above).

Another approach to bind the biological coating to the surface with functional polymer is e.g. esterification. Such binding process may be useful if the biological coating is based on phosphorylcholine (two -OH groups of the polymer coating and of the biological coating are esterified, i.e. bind to each other whilst a H_2O group is removed). A further possibility to bind the biological coating to the polymer coating is acid amide formation. For the purpose of illustration, an example how a polyallylamine as the functional polymer may bind to phosphorylcholine as biological coating is given here:



(Phosphorylcholine) (Polyallylamine)

People skilled in the art will be aware of further suitable mechanisms suited for the specific biological coating used.

In general, the biological coating may be applied to the polymer coating according to any prior art technique. This has particularly the advantage that, in order to practice the present invention, not the complete coating process has to be adapted, but only the plasma polymerization step.

As will already be apparent from the foregoing, several functional groups are useful to fulfil the need of the present invention. What is, in general, required is a chemically active group, i.e. a group which is responsive to substitution or rearrangement (suitable mechanisms are e.g. amide formation, amine formation, esterification, etherification, etc.). For example, any halogen group would be suited as a functional group, whereas a methyl group would not be.

An important, but not strictly required, property of the present invention is that the functional groups bound to the monomeres are stable, even after the plasma polymerization or grafting process. For example, the $-NH_2$ group of the created functional polymer does not react with other chemical substances after the plasma coating process. Therefore, it is possible to apply the biological coating at a later point in time or even at a different location, which in turn makes the process and the handling easier.

The invention also relates to an apparatus for performing the method according to the present invention. In general, most of the components of the apparatus are elements commonly used to perform plasma polymerization or plasma grafting. However, a container has to be provided filled with a chemical agent consisting of monomer molecules chemically combined with functional groups, said chemical agent being present at least in its gaseous state, wherein said container is lockably connected with said chamber. The locking means may e.g. be a valve. In this combination, the required functional monomer may be provided to the reaction or discharge chamber. Further containers may be provided for a chemically active gas (for the purification step) or for an inert gas (in case plasma grafting is intended).

According to a further, preferred embodiment of the present invention, a shelf or rack in said chamber is provided for suspending or hanging of medical devices. This is particularly useful if intravascular blood gas sensors have to be coated, which should not be in contact with the walls of the chamber, in order to provide a complete coating on its whole surface.

The present invention further relates to the use of a chemical agent consisting of monomer molecules chemically combined with functional groups, or of a monomer mixed with a substance which, under the influence of electromagnetic radiation or of charge carriers, forms a functional group which binds chemically to said monomer, for pretreatment of a medical device prior to appliance of a biological coating.

The invention will now be described, by way of a non-limiting example and with reference to the

accompanying drawings, in which:

Figs. 1-3 depict the schematics of an intravascular blood gas sensor which needs to be coated with a biological coating, wherein

Fig. 1 shows the basic arrangement of an intravascular blood gas measuring system,

Fig. 2 is a longitudinal section of a single sensor forming part of the probe,

Fig. 3 is a longitudinal section of the probe tip,

Figs. 4-6 depict suitable chemical agents to practice the invention,

Fig. 7 depicts the result of a plasma polymerization process,

Fig. 8 depicts the result of a plasma grafting process, and

Fig. 9 depicts a suitable apparatus for practising the invention.

Fig. 1 depicts a system for the invasive measurement of blood parameters, for example of the partial carbon dioxide pressure (pCO_2) or the pH value. The light of an optical transmitter 1 is directed into an optical fiber 2 (see arrow 2a). Preferably, this is a glass fiber. Usually a train of light pulses is used, but this is not a strict requirement. The light passes an optical coupler 3 and reaches tip 4 of the sensor, said tip being intended for introduction into the artery of a patient. Tip 4 of the sensor contains a gel into which a dye such as phenol red is immobilized. Said dye modifies at least one optical parameter, preferably the intensity, of the light depending on the pCO_2 (or, in other cases, the pO_2 or the pH) value of the blood. The modified light is reflected into the same fiber and, after passing through optical coupler 3, reaches an optical receiver 5 (see arrow 5a). It is understood that optical transmitter 1 and optical receiver 5 are incorporated in a monitor or other measuring instrument. Dashed line 6 indicates a releasable connection between the probe 7 and the monitor 8. The optical probe consists of a multiplicity of sensors and the related number of optical fibers; preferably, it comprises 3 sensors responsive to pO_2, pCO_2 and pH.

Operation of a single sensor will now be explained by means of Fig. 2 which shows a longitudinal section through a pH sensor. The mechanical construction of the pH sensor is typical for sensors of this type; the pO_2 and the pCO_2 sensor have a similar construction.

According to Fig. 2, the pH sensor comprises a glass fiber 9 and an optical reflector 10. Optical reflector 10 is made of stainless steel. Between the optical fiber 9 and the reflector 10, a gel 11 is located. This gel is used to immobilize a dye such as phenol red, the optical characteristics of which varies with the blood parameter - in this case, pH - to be measured. The surface 10a of the optical reflector 10 facing the gel 11 is polished.

The sensor is surrounded by a semi-permeable or selective membrane 12 which is fastened on the sensor by means of a glue 13. As Fig. 2 depicts, the glue is only introduced at the distal end of the sensor (left side in Fig. 2) and at the very proximal end. The selective membrane is permeable to the ions or gas molecules to be measured. In case of the pH sensor shown in Fig. 2, the selective membrane is permeable to H^+ ions.

Fig. 3 depicts a longitudinal section of the probe tip 14 of an optical probe comprising three sensors, according to prior art design. A sheath 15 is closed at its outer end (proximal end) by a metal cap 16 and connected, as shown by 17, with a tubing element 18. The connection between sheath 15 and tubing element 18 is secured by adhesive means. Tubing element 18 ends (not shown) at a connector for connection to an appropriate monitor.

Sheath 15 contains three sensors, two of which are shown in Fig. 3, namely a pH sensor 19 and a pCO_2 sensor 20. A third sensor, namely a pO_2 sensor, is not shown in Fig. 3 as it is hidden behind pCO_2 sensor 20.

Each of the sensors is connected with the associated monitor via an optical fiber, as shown by optical fiber 21 (which is surrounded by an appropriate envelope 22) for the case of pH sensor 19 in Fig. 3; likewise, reference number 23 relates to the optical fiber of pCO_2 sensor 20, and reference number 24 to the envelope of this fiber.

The various sensors are fastened within sheath 15 by means of a silicone glue or adhesive 25. Sheath 15 further comprises three openings, the first of which is labeled as 26 in Fig. 3, whereas the second opening 27 is hidden behind the pCO_2 sensor 20. The third opening is not shown in Fig. 3; it is contained in the broken-away part. These openings ensure that, when the probe tip is introduced into a patient's artery, the sensors are in contact with the blood thus allowing gas molecules and hydrogen ions to reach the sensors.

PCO_2 sensor 20 further comprises a dye-containing gel 28 and an optical reflector 29. The region where dye-containing gel 28 is located is also called "diffusion zone". Sensor 20 is, insofar as contained in sheath 15, surrounded by a semi-permeable membrane 30 which is fixed on optical fiber 23 and reflector 29 by means of a further glue or adhesive.

In similar manner, pH sensor 19 comprises a dye-containing gel 31, a reflector 32 and a semi-

permeable membrane 33.

It is understood that the probe depicted in Fig. 3 is only a typical example for an invasive optical blood parameter probe. In other embodiments, the probe may comprise less sensors or even more elements, such as a strain relieving wire.

As the probe is intended for insertion into a blood vessel, typically the arteria radialis or the arteria femoralis, and therefore is in blood contact over several hours or even days, a biological or bioactive coating is required in order to avoid that the blood clots attach to the sensor or the surrounding catheter and thus impact the measurement or cause thrombosis.

In a specific embodiment, the probe tip or the whole sensor is exposed to an oxygen atmosphere in a pressure-tight chamber. The chamber may be part of a usual plasma polymerization or plasma grafting equipment. The pressure in the chamber is then considerably reduced to 0.7 millibar ($7 \cdot 10^{-4}$ bar) Thereafter, a source of radiation is turned on which emits RF (radio frequency) waves into the chamber. In the present embodiment, a frequency of 13.56 MHz has been used and a transmitter power of 90 mW (milliwatts); the radiation source was turned on for a duration of 5 minutes. This first step sparks or "burns" impurities on the surface of the probe. Further, charge carriers are generated in the outer surface of the probe.

In a second step, argon is used to flush the oxygen out of the chamber. The radiation transmitter is still operating, also at a power of 90 mW. The pressure in the chamber is further reduced to 0.2 millibar ($2 \cdot 10^{-4}$ bar) The radiation source is operated for 5 minutes during this second step.

The purpose of this treatment with argon under spark discharge is to create further charge carriers, and to make the charge carriers already created in the first step "quasi-permanent".

When the second step is completed, the source of radiation is switched off. In a third step, allylamine is fed into the chamber and flushes the argon out. The charge carriers in the outer surface of the probe initiate the polymerization process. The allylamine molecules polymerize on the surface of the probe (but not in the gaseous environment); due to the charge carriers in the surface, the ends of a multiplicity of the polymer chains attach to the surface, such that the generated polymer coating is in "chemical" contact with the surface (which in turn inhibits removal of the plasma coating). The outer ends of the polymer chains carry free and stable amino groups (NH_2).

The probe may now be removed from the chamber and coated with a biological coating in basically known manner.

The process described above is the plasma grafting process. In the case of plasma polymerization, the second step (argon flushing) is not performed, and a monomer is fed into the chamber for 20 minutes at a pressure of 0.3 millibar ($3 \cdot 10^{-4}$ bar).

Fig. 4 depicts a selection of suitable carboxylic compounds (monomer with carboxyl group) suitable as chemical agents in the third step. The general formula is given in Fig. 4(a), wherein $(CH_2)_n$ denotes an arbitrary number of CH_2 groups, $n = 0$ or an integer. Figs. 4(b) to 4(c) illustrate some agents out of this group; e.g., Fig. 4(b) is acrylic acid, Fig. 4(c) is butenoic acid and Fig. 4(d) is pentenoic acid.

Likewise, Fig. 5(a) shows the general formula for agents with an amino group. Specific examples of this group of substances are: Allylamine (Fig. 5(b)) and 4-amino-1-butene (Fig. 5(c)).

Fig. 6(a) is the general formula of suitable alcohols (compounds with an - OH group); Fig. 6(b) depicts a typical example of this group, allyl alcohol.

The difference between the plasma polymerization technique and the plasma grafting technique is shown in Fig. 7 and 8. Fig. 7 shows a plasma polymer 34 with free amino ($-NH_2$) groups (at every 2nd carbon atom in the polymer chain) on the surface 35 of an intravascular probe obtained with the plasma polymerization technique. In contrast, the result of the plasma grafting technique is depicted in Fig. 8. The ends of the plasma grafted chains 36 adhere to the surface 37, as depicted by reference number 38. This is a covalent bonding which provides better contact between polymer and surface and reduces the probability of detachment of the polymer. Further, the polymer chains in the environment of Fig. 8 are generally shorter.

The basics of an apparatus for performing the inventive method is shown in Fig. 9. A pressure-tight, electrically shielded chamber 39 contains a shelf or rack 40 for pinning up of intravascular probes. The front opening 41 may be closed by a suitable door (not shown).

A pump 42 is used to obtain the required low pressure. It is connected via tube 43 to back wall 44 of chamber 39. The source of radiation is depicted as 45.

Three openings 46, 47 and 48 are provided as inlets for oxygen, argon and allylamine (or polyacrylic acid), respectively. These openings are connected via tubes 49, 50 and 51 to respective containers 52, 53 and 54 holding these gases, or volatile liquids.

Claims

1. Method of pretreating the surface of a medical device for appliance of a biological coating, characterized by the steps of:
   (1.1) exposing said medical device to a chemical agent consisting of monomer molecules chemically combined with functional groups, or of a monomer mixed with a substance which, under the influence of electromagnetic radiation, forms a functional group which binds chemically to said monomer, said chemical agent being present at least in its gaseous state,
   (1.2) irradiating electromagnetic waves, in particular of the radio frequency range, into said chemical agent and/or onto the surface of said medical device until the molecules of said chemical agent constitute a functional polymer on the surface of said medical device.

2. Method for applying a biological coating to the surface of a medical device intended for blood contact, characterized by the steps of:
   (2.1) exposing said medical device to a chemical agent consisting of monomer molecules chemically combined with functional groups, or of a monomer mixed with a substance which, under the influence of electromagnetic radiation, forms a functional group which binds chemically to said monomer, said chemical agent being present at least in its gaseous state,
   (2.2) irradiating electromagnetic waves, in particular in the radio frequency range, into said chemical agent and/or onto the surface of said medical device until the molecules of said chemical agent constitute a functional polymer on the surface of said medical device,
   (2.3) applying said biological coating to the surface of said medical device.

3. Method of pretreating the surface of a medical device for appliance of a biological coating, characterized by the steps of:
   (3.1) exposing said medical device to an inert gas,
   (3.2) irradiating electromagnetic waves, in particular of the radio frequency range, into said inert gas and/or onto the surface of said medical device,
   (3.3) exposing said medical device to a chemical agent consisting of monomer molecules chemically combined with functional groups, or of a monomer mixed with a substance which, under the influence of charge carriers created during step (3.2), forms a functional group which binds chemically to said monomer, said chemical agent being present at least in its gaseous state, until the molecules of said chemical agent constitute a functional polymer on the surface of said medical device.

4. Method for applying a biological coating to the surface of a medical device intended for blood contact, characterized by the steps of:
   (4.1) exposing said medical device to an inert gas,
   (4.2) irradiating electromagnetic waves, in particular of the radio frequency range, into said inert gas and/or onto the surface of said medical device,
   (4.3) exposing said medical device to a chemical agent consisting of monomer molecules chemically combined with functional groups, or of a monomer mixed with a substance which, under the influence of charge carriers created during step (4.2), forms a functional group which binds chemically to said monomer, said chemical agent being present at least in its gaseous state, until the molecules of said chemical agent constitute a functional polymer on the surface of said medical device,
   (4.4) applying said biological coating to the surface of said medical device.

5. Method according to any of the preceding claims, characterized in that said chemical agent is contained in a closed chamber (39) which also contains said medical device.

6. Method according to claim 5, characterized in that said chamber (39) is pressure-tight and that a pressure below atmospheric pressure is applied to said chamber.

7. Method according to claim 6, characterized in that the pressure in said chamber (39) is approximately a vacuum, in particular in the range of 10^{-5} bar to 10^{-2} bar and more specifically in the range of 10^{-4} bar to 10^{-3} bar.

8. Method according to any of the preceding claims, characterized in that said monomer comprises molecules consisting of at least two carbon atoms combined by double bond.

9. Method according to any of the preceding claims, characterized in that said functional group in said molecules of said chemical agent is an amino group.

10. Method according to claim 9, characterized in that said chemical agent is allylamine, 4-amino-1-butene or any other olefin with additional amino group, or a combination of olefin and ammonium hydroxyde.

11. Method according to any of claims 1 to 8, characterized in that said functional group in said molecules of said chemical agent is a carboxyl group.

12. Method according to claim 11, characterized in that said chemical agent is one selected of the group of carboxylic acids, in particular acrylic acid, butenoic acid, or pentenoic acid.

13. Method according to any of claims 1 to 8, characterized in that said functional group in said molecules of said chemical agent is an OH group.

14. Method according to claim 13, characterized in that said chemical agent is ally alcohol.

15. Method according to any of the preceding claims, characterized by the additional steps of
(15.1) exposing said medical device to a chemically active gas, in particular oxygen,
(15.2) irradiating electromagnetic waves into said chemically active gas and/or onto the surface of said medical device until the surface of said medical device is substantially clean of impurities,
wherein said steps are performed prior to exposing said medical device to said chemical agent.

16. Method according to any of the preceding claims, characterized by the step of applying said biological coating to the polymerized surface of said medical device by means of esterification, acid amide formation, acid amine formation, or etherification.

17. Method according to any of the preceding claims, characterized in that said medical device is an intravascular blood gas sensor.

18. Apparatus for pretreatment of the surface of a medical device for appliance of a biological coating, said apparatus comprising a pressure-tight chamber (39) with a releasable lock for insertion of said medical device and with a source (45) of electromagnetic radiation, preferably in the radio frequency range, for performing plasma polymerization, characterized by a container (54) filled with a chemical agent consisting of monomer molecules chemically combined with functional groups, or consisting of a monomer mixed with a substance which, under the influence of electromagnetic radiation or of charge carriers, forms a functional group which binds chemically to said monomer, said chemical agent being present at least in its gaseous state, said container (54) being lockably connected with said chamber (39).

19. Apparatus according to claim 18, characterized by a second container (52;53) filled with a chemically active gas or an inert gas and being lockably connected with said chamber.

20. Apparatus according to claim 18 or 19, characterized by a shelf or rack (40) in said chamber (39) suited for suspending or hanging of said medical devices, in particular intravascular blood gas sensors.

21. Use of a chemical agent consisting of monomer molecules chemically combined with functional groups, or of a monomer mixed with a substance which, under the influence of electromagnetic radiation or of charge carriers, forms a functional group which binds chemically to said monomer, for pretreatment of a medical device prior to appliance of a biological coating.

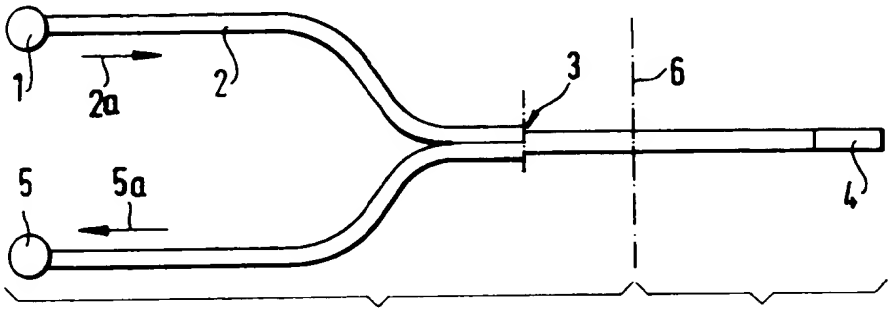


Fig. 1

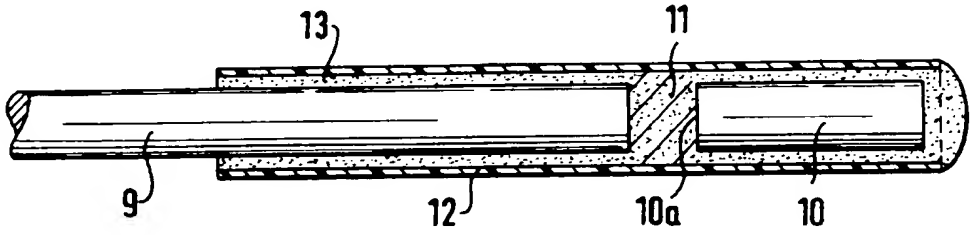


Fig. 2

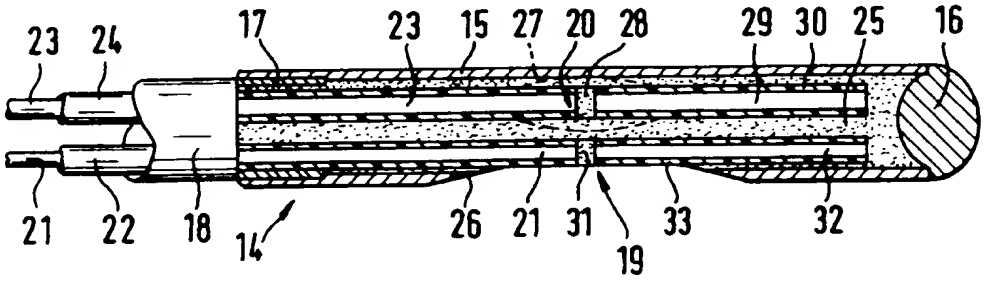


Fig. 3

Fig. 4a

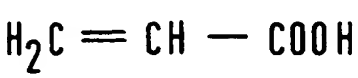


Fig. 4b

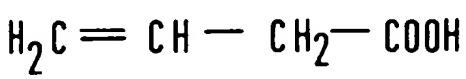


Fig. 4c

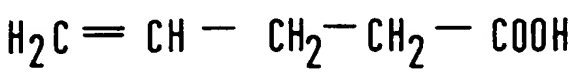


Fig. 4d

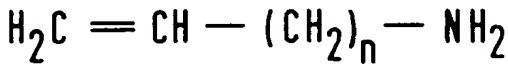


Fig. 5a

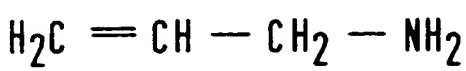


Fig. 5b

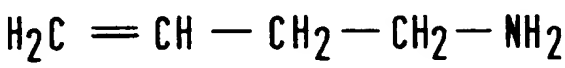


Fig. 5c

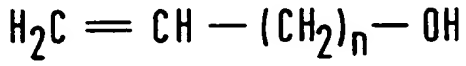


Fig. 6a

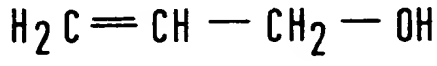
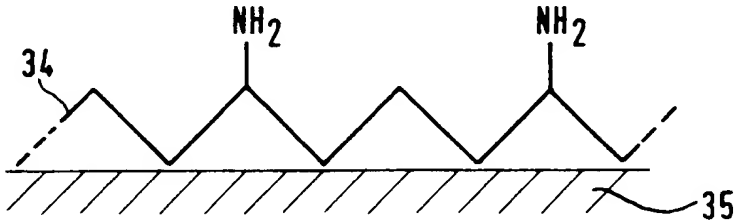


Fig. 6b

Fig. 7



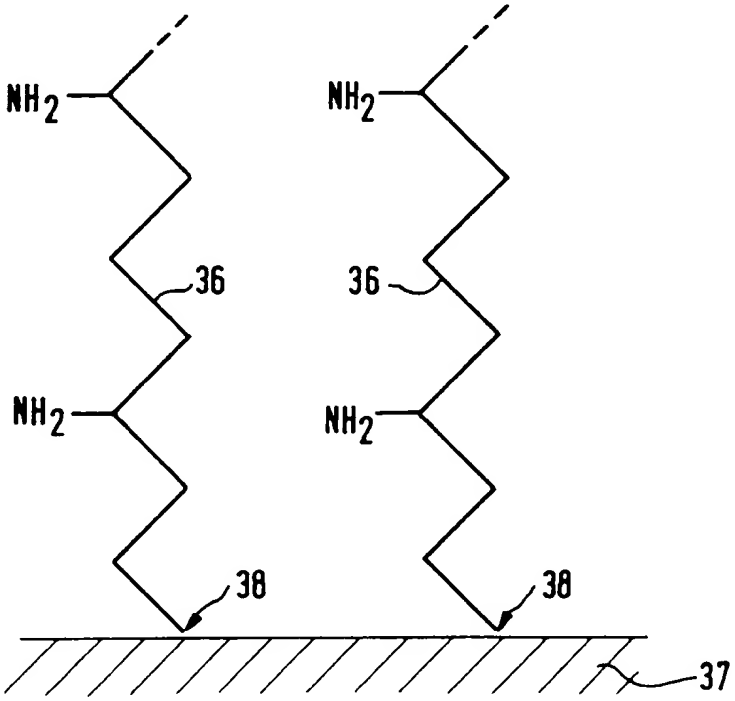
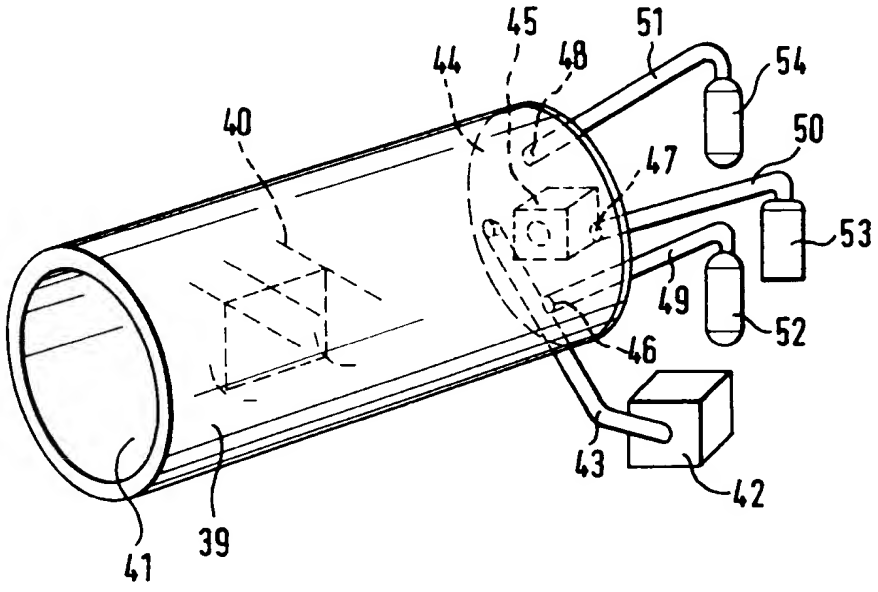


Fig. 8

Fig. 9



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EUROPEAN SEARCH REPORT

Application Number

EP 91 10 8146

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	EP-A-0 294 905 (SENTRON) * column 4, line 44 - line 58 *	1	A61L33/00
A	EP-A-0 124 200 (BECTON DICKINSON) * claims 1,3,5 *	1	
A	EP-A-0 352 199 (TERUMO) * page 4, line 11 - line 22; claim 6 *	1	
A	WO-A-8 911 919 (BIOGOLD)		
A	WO-A-8 700 060 (BATTELLE)		
A	US-A-4 919 659 (T.A.HORBETT)		
			TECHNICAL FIELDS SEARCHED (Int. Cl.5) A61L

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	22 JANUARY 1992	PELTRE CHR.

CATEGORY OF CITED DOCUMENTS

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